EPA/EPO/OEB
D-80298 München
+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 2	Directorate General 2	Direction Générale 2

Dzieglewska, Hanna Eva
Frank B. Dehn & Co.
St Bride's House
10 Salisbury Square
London EC4Y 8JD
ROYAUME-UNI

Telephone numbers:	Branch at The Hague
Primary Examiner (substantive examination)	+31 70 340-3263
Formalities Officer / Assistant (Formalities and other matters)	+31 70 340-0

Application No.	Ref.	Date
03 745 226.5 - 1216	27.68.85733	16.11.2007
Applicant: MEDVET SCIENCE PTY. LTD.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

Bayrak, Sinasi
Primary Examiner
for the Examining Division

Enclosure(s): 6 page/s reasons (Form 2906)
XP002992506

Registered Letter
EPO Form 2001 07.02CSX

The examination is being carried out on the **following application documents**:

Description, Pages

1-58 as published

Sequence listings, Pages

1-6 as published

Claims, Numbers

1-49 as published

Drawings, Sheets

1/21-19/21	as published			
20/21, 21/21	received on	29.10.2004	with letter of	29.10.2004

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

D1: MACHWATE M. ET AL.: 'Sphingosine kinase mediates cyclic AMP suppression of apoptosis in rat periosteal cells' MOLECULAR PHARM. vol. 54, 1998, pages 70 - 77, XP008043223

D2: WO 99 12533 A

D4: WO 02 098458 A

D5: WO 01 85953 A

D6: BLAUKAT A. ET AL.: 'Activation of sphingosine kinase by the bradykinen B2 receptor and its implication in regulation of the ERK/MAP kinase pathway' BIOL. CHEM. vol. 382, January 2001, pages 135 - 139, XP008043225

D7: CUVILLIER O. ET AL.: 'Sphingosine-1-phosphate antagonizes apoptosis of human leukemia cells by inhibiting release of cytochrome c and Smac/DIABLO from mitochondria' BLOOD vol. 98, no. 9, November 2001, pages 2828 - 2836, XP008043224

The following document (D) is cited by the examiner (see the Guidelines, C-VI, 8.7). A

copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D3: PU XIA. ET AL.: 'Sphingosine kinase Interacts with TRAF2 and Dissects Tumor Necrosis Factor-alpha Signaling' J. Biol. Chem vol. 277, 2002, pages 7996-8003, XP002992506

1 CLARITY (Art. 84 EPC) AND LACK OF DISCLOSURE (Art. 83 EPC)

1.1 Claims 1-9, 12-20,28-36, 44-47 relate to compounds defined by reference to a desirable characteristic or property or the invention is defined by a result to be achieved, namely "an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of said sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase activity and inhibiting or otherwise antagonising said phosphorylation down-regulates sphingosine kinase activity", "an agent for a time and under conditions sufficient to modulate the phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity", "wherein said phosphorylation is modulated at S225", "wherein said agent binds, links or otherwise associates with S225", "wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation", "wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation", "which agent modulates phosphorylation of sphingosine kinase", "An isolated sphingosine kinase variant comprising a mutation in a region of said sphingosine kinase which region comprising a phosphorylation site, wherein said variant exhibits ablated or reduced phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof", "An isolated sphingosine kinase variant comprising a mutation in a region of said sphingosine kinase which region comprising a phosphorylation site, wherein said variant exhibits ablated or reduced phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof", "An isolated sphingosine kinase variant comprising a mutation in a region of said sphingosine kinase which region comprising a phosphorylation site, wherein said variant exhibits enhanced or up-regulated phosphorylation capacity relative to wild-type sphingosine

kinase or a functional derivative, homologue or analogue thereof".
Respective claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds. Consequently, the claims lack support and the application lacks disclosure. Independent of the above reasoning, the claims also lack clarity because the features used in said claims are unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 84 EPC).

1.2 Second medical use claims 29-40,42,43 are not acceptable under Art. 84 EPC. The therapeutic application is functionally defined ("a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase activity", "which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity") by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease) (C-IV, 4.2).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition (C-III, 6.5).

2 PATENTABILITY (Art. 52 EPC)

2.1 Claims 12-27 are directed to a method for treatment of the human or animal body by therapy which is not susceptible of industrial application. Such subject-matter is expressly excluded from patentability by Art. 52 (4) EPC and thus the said claims are as such not allowed.

3 NOVELTY (Art. 54 EPC)

3.1 INDEPENDENT CLAIMS 1,2,12,13,28,29,44-47

3.2 The present application appears not to meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1,2,12,13,28,29,44-47, insofar as clear and acceptable under Art. 52 (4), is not new in the sense of Article 54(1) and (2) EPC:

Document D1 discloses a method of modulating sphingosine kinase functional activity, said method comprising contacting sphingosine kinase with an effective amount of an agent (**PD98059**, or DMS, forskolin; and also mentioned are other sphingosine kinase modulating agents such PDGF, serum, 12-O-tetradecanoylphorbol-13-acetate, U937, ceramide) for a time and under conditions sufficient to modulate sphingosine kinase. In addition, document D1 discloses a method of modulating cellular activity (e.g. apoptosis), said method comprising contacting said cell with an effective amount of an agent (PD98059) for a time and under conditions sufficient to modulate sphingosine kinase and the cellular activity. The applicant's attention is drawn to the fact that **PD98059** is claimed in claim 11 of the present application and is thus an agent that modulates **phosphorylation** of sphingosine kinase.

Document D2 discloses a method of modulating sphingosine kinase functional activity/modulating cellular activity, said method comprising contacting said sphingosine kinase with an effective amount of an agent (**HDL**) for a time and under conditions sufficient to modulate said sphingosine kinase (see page 33, line 5-10, Fig. 3D).

Document D3 discloses a method of modulating sphingosine kinase functional activity/modulating cellular activity (apoptosis), said method comprising contacting said sphingosine kinase with an effective amount of an agent (**TRAF2**) for a time and under conditions sufficient to modulate said sphingosine kinase (see page 7997, column 2- page 7999, column 1, par. 1).

The PCT application WO02098458 (D4) published on 12. 12. 2002 claims the priority date of 07. 06. 2001. It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 22, paragraph 1 or Article 39, paragraph 1 of the Co-operation Treaty has been paid. The requirements of Article 158(2) EPC are thus fulfilled.

Its content as filed is therefore considered as comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) and (4) EPC. This earlier application shows, as document D3, a method of modulating sphingosine kinase functional activity/modulating cellular activity (apoptosis), said method comprising contacting said sphingosine kinase with an effective amount of an agent (**TRAF2**) for a time and under conditions sufficient to modulate said sphingosine kinase (see Example 2).

Thus, it is prejudicial to the novelty of the subject-matter of claims 1,2,12,13,28,29,44-45 of the present application insofar as the same Contracting States are designated.

Document D5 discloses a method of modulating cellular activity (cell growth) of a cell, said method comprising contacting said cell with an effective amount of an agent for a time and under conditions sufficient to modulate the functional activity of sphingosine kinase (see the examples).

Agents that modulate sphingosine kinase functional activity/modulating cellular activity are also disclosed in D6 and D7 (see the entire documents).

The applicant's attention is drawn to the fact that

(I) the feature present claims 44 and 45 "which agent modulates phosphorylation of sphingosine kinase.." is of no relevance insofar as the pharmaceutical composition/agent per se is concerned. Therefore, the subject matter of said claims is anticipated by any document disclosing " a pharmaceutical composition comprising an agent" or "an agent" (see e.g. D1: PD98059; D2: HDL).

(ii) in view of the above cited prior art, the present invention appears to be based on a discovery (the fact phosphorylation of sphingosine kinase at S225 in hSK1 is required for the translocation) that appears to provide an explanation for the mechanism of action of the sphingosine kinase modulating agents as clearly defined in the application (e.g. PD98059) and their use in the known modulation of cellular activity and treatment/prevention of diseases associated with aberrant cellular activity (e.g. neoplasms) . In the present case, demonstrating that phosphorylation of sphingosine kinase at S225 in hSK1 is required for the translocation cannot confer novelty to the use of a known compound (e.g. PD98059) for a known purpose (modulating sphingosine kinase/ cellular activity) or for known therapeutic uses of such compounds; see decision of the Board of Appeals T254/93.

4 INVENTIVE STEP (Art. 56 EPC)

4.1 INDEPENDENT CLAIMS 1,2,12,13,28,29,44-47

4.2 Should the applicant be able to overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated as the present subject-matter of claims 1,2,12,13,28,29,44-47, as far as novel, appears obvious with regard to the documents D1-3,5-7 (Art. 56 EPC). The use sphingosine kinase modulating agent to influence cellular activity, such as aberrant cell growth, appears to have been well known in the art.

5 DEPENDENT CLAIMS

5.1 Dependent claims 2-11,14-27,30-43 appear not to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC in respect of novelty and/or inventive step (Articles 54 and 56 EPC).

6 REMARKS

6.1 If the applicant wishes to file amended claims, the attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC).

6.2 In order to facilitate the examination of the conformity of the amended application with the requirements of article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based. If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

P.B.5818 - Patentlaan 2
2280 HV Rijswijk (ZH)
(070) 3 40 20 40
FAX (070) 3 40 30 16

Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 1	Directorate General 1	Direction générale 1

Dzieglewska, Hanna Eva
Frank B. Dehn & Co.
St Bride's House
10 Salisbury Square
London EC4Y 8JD
GRANDE BRETAGNE

EPO Customer Services
Tel.: +31 (0)70 340 45 00

Date
08.05.06

Reference	Application No./Patent No.
27.68.85733	03745226.5 - 1216 PCT/AU0300388

Applicant/Proprietor
MEDVET SCIENCE PTY. LTD.

Notice drawing attention to Article 86(2) EPC, Art. 2 No. 5 of the rules relating to fees
- Payment of the renewal fee plus additional fee -

The renewal fee for the 04. year fell due on 31.03.06 unless this date falls within the period covered by an interruption of the proceedings in accordance with Rule 90(1) EPC.

The amount of the renewal fee on that date was **EUR 425,00** (see OJ EPO 2001, 374, 377, 378, and 543).

The renewal fee was not paid by the due date.
The renewal fee may still be validly paid **up to the last day of the sixth calender month** following the due date, provided that the additional fee (10% of the renewal fee) is paid at the same time.

Within the above period which cannot be extended the following fees are to be paid:

Renewal fee for the 04. year:	EUR	425,00
Additional fee:	EUR	42,50
TOTAL AMOUNT	EUR	467,50

If the renewal fee and the additional fee are not paid in due time, the European patent application shall be deemed to be withdrawn (Art.86(3) EPC).

Note to users of the automatic debiting procedure:
The normal time limit for payment of the above renewal fee had already expired when the automatic debit order was received. The renewal fee and the surcharge will be debited automatically on the last day of the period of grace (Supplement to OJ EPO 2/1999; OJ EPO 2000, 62).

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

FRANK B. DEHN & CO.

Patent and Trade Mark Attorneys

179 Queen Victoria Street, London EC4V 4EL, England
Telephone: +44 (0)20 7206 0600 Fax: +44 (0)20 7206 0700
E-mail: mail@frankbdehn.com Web: www.frankbdehn.com

CONFIRMATION OF FAX

European Patent Office
D-80298 München
Germany

date 15 March 2006
your ref
our ref 4.-

BY FACSIMILE

EPO - Munich
3
17. März 2006

Dear Sirs

Change of address

Please note that the London office of Frank B. Dehn & Co. will be closed this coming Friday, 17th March, and will re-open on Monday, 20th March at our new location:

Frank B. Dehn & Co.
St Bride's House
10 Salisbury Square
London
EC4Y 8JD

Telephone +44 20 7632 7200
Fax: +44 20 7353 8895

Please note that on certain application forms the direct telephone number may be given as +44 1273 244200, +44 1865 305100, or 089 2422 8130, and all of these numbers remain unchanged. All occurrences of +44 20 7206 0600, however, are to change to +44 20 7632 7200.

Please ensure that all communications on European patent matters, on PCT applications filed via the EPO and on PCT Chapter II matters are directed to our new address from Monday. If a listing of the professional representatives affected is required, please urgently let me know.

Please also record the change of contact details on our deposit account no. 28050069.

Yours faithfully
Frank B. Dehn & Co.

D. P. Matthews

FRANK B. DEHN & CO.

Patent and Trade Mark Attorneys

179 Queen Victoria Street, London EC4V 4EL, England
Telephone: +44 (0)20 7206 0600 Fax: +44 (0)20 7206 0700
E-mail: mail@frankbdehn.com Web: www.frankbdehn.com

CONFIRMATION OF FAX

European Patent Institute
Institute of Professional Representatives
before the European Patent Office
Postfach 26 01 12
D-80058 Munich
Germany

date 15 March 2006
your ref
our ref 4.-

BY FACSIMILE

EPO - Munich
3
17. März 2006

Dear Sirs

Change of address

Please note that the London office of Frank B. Dehn & Co. will be closed this coming Friday, 17th March, and will re-open on Monday, 20th March at our new location:

Frank B. Dehn & Co.
St Bride's House
10 Salisbury Square
London
EC4Y 8JD

Telephone +44 20 7632 7200
Fax: +44 20 7353 8895

Please update your records accordingly. If a listing of the professional representatives affected is required, please let me know.

Yours faithfully
Frank B. Dehn & Co.

D. P. Matthews